

REVIEW | *Liver and Biliary Tract Physiology/Pathophysiology*

Bile acid receptors FXR and TGR5 signaling in fatty liver diseases and therapy

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Chiang JYL, Ferrell JM. Bile acid receptors FXR and TGR5 signaling in fatty liver diseases and therapy. *Am J Physiol Gastrointest Liver Physiol* 318: G554–G573, 2020. First published January 27, 2020; doi:10.1152/ajpgi.00223.2019.—Bile acid synthesis is the most significant pathway for catabolism of cholesterol and for maintenance of whole body cholesterol homeostasis. Bile acids are physiological detergents that absorb, distribute, metabolize, and excrete nutrients, drugs, and xenobiotics. Bile acids also are signal molecules and metabolic integrators that activate nuclear farnesoid X receptor (FXR) and membrane Takeda G protein-coupled receptor 5 (TGR5; i.e., G protein-coupled bile acid receptor 1) to regulate glucose, lipid, and energy metabolism. The gut-to-liver axis plays a critical role in the transformation of primary bile acids to secondary bile acids, in the regulation of bile acid synthesis to maintain composition within the bile acid pool, and in the regulation of metabolic homeostasis to prevent hyperglycemia, dyslipidemia, obesity, and diabetes. High-fat and high-calorie diets, dysbiosis, alcohol, drugs, and disruption of sleep and circadian rhythms cause metabolic diseases, including alcoholic and nonalcoholic fatty liver diseases, obesity, diabetes, and cardiovascular disease. Bile acid-based drugs that target bile acid receptors are being developed for the treatment of metabolic diseases of the liver.

bile acid metabolism; bile acid therapies; farnesoid X receptor; alcoholic and nonalcoholic fatty; liver diseases; Takeda G protein-coupled receptor 5

INTRODUCTION

Emerging research in the last two decades has identified bile acids as important nutrient sensors and metabolic integrators that play a critical role in maintaining metabolic homeostasis. Bile acids are physiological detergents needed for absorption of dietary fat, steroids, and lipid-soluble vitamins, and are also signal molecules and endogenous ligands that activate nuclear farnesoid X receptor (FXR) and membrane Takeda G protein-coupled receptor 5 (TGR5, i.e., G protein-coupled bile acid receptor-1) (22). Bile acid signaling through these two major bile acid receptors plays a critical role in integrating glucose, lipid, and energy metabolisms (25, 27). Bile acid synthesis is the most significant pathway for the catabolism of cholesterol and is responsible for the daily output of ~90% cholesterol in the body (166). Primary bile acids synthesized in the liver are secreted into bile, stored in the gallbladder, and released to the gastrointestinal tract after food intake. Bile acids are reabsorbed mostly in the ileum and are transported back to the liver via portal blood circulation to regulate bile acid synthesis and homeostasis. The enterohepatic circulation of bile acids is an important physiological mechanism for maintaining whole

body glucose, lipid, and energy homeostasis to prevent hyperglycemia, dyslipidemia, and obesity, and it protects against inflammatory metabolic diseases of the digestive and cardiovascular systems (27). The bile acid-mediated integration of metabolic regulation is very complex and not completely understood. Most studies of bile acid metabolism and regulation rely on using genetically modified mice fed various high-fat diets to induce obesity, insulin resistance, and fatty liver disease. The study of bile acid metabolism in animal models has been translated to therapeutic treatment of obesity, diabetes, and nonalcoholic fatty liver disease in human patients (106). This review will provide an update on the recent advances in understanding the role and mechanism of bile acid receptor signaling in metabolic regulation and pathogenesis of fatty liver diseases and advances in bile acid-based drug therapies for metabolic diseases of the liver. Most references cited were published from 2000 to 2020, and older original articles can be found in the review articles cited.

BILE ACID SYNTHESIS AND METABOLISM

Bile Acid Synthesis in the Liver: Classic and Alternative Pathways

Bile acid synthesis is remarkably similar between humans and mice, but bile acid composition and pool size vary markedly between rodents and humans (27). These differences may

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be due to differential utilization of the two bile acid synthesis pathways, the anatomic difference of the gastrointestinal tract, the gut microbiota, and the enterohepatic circulation of bile acids. There are 2 major bile acid synthesis pathways catalyzed by 17 enzymatic reactions. The classic bile acid synthesis pathway is initiated by cholesterol 7 α -hydroxylase (CYP7A1), the only rate-limiting enzyme to synthesize the two primary bile acids, cholic acid (CA) and chenodeoxycholic acid (CDCA), in the human liver (Fig. 1). CYP7A1 converts cholesterol to 7 α -hydroxycholesterol, which is then converted to 7 α -hydroxy-4-cholesten-3-one (C4) by a hydroxy steroid dehydrogenase. C4 is the common precursor for synthesis of CA and CDCA. Serum C4 levels reflect the rate of bile acid synthesis and are used as a biomarker for the rate of bile acid synthesis in the liver. Sterol 12 α -hydroxylase (CYP8B1) is a branching enzyme that hydroxylates C4 and produces CA. Without CYP8B1, C4 is converted to CDCA. Mitochondrial sterol 27-hydroxylase (CYP27A1) catalyzes a steroid side-chain oxidation in preparation for a peroxisomal β -oxidation reaction that cleaves a propionyl-CoA to form cholyl-CoA and chenodeoxycholyl-CoA, respectively (Fig. 1). Bile salt CoA-synthase (BACS) activates recycled CA and CDCA, and bile acid intermediates in hepatocytes to cholyl-CoA and chenodeoxycholyl-CoA, which are then conjugated to the amino acids taurine (T) or glycine (G) by bile acid-CoA-to-amino acid N-acyltransferase (BAAT), forming T/G-CA and T/G-CDCA.

The alternative bile acid synthesis pathway is initiated by CYP27A1 and converts cholesterol to 27-hydroxycholesterol [also known as 25(R)-26-hydroxycholesterol] and 3 β -hydroxy-5-cholestenic acid, which are then hydroxylated at the 7 α position by oxysterol 7 α -hydroxylase (CYP7B1) (Fig. 1).

CYP27A1 and CYP7B1 are widely expressed in extrahepatic tissues, including steroidogenic tissues and macrophages. The most abundant circulating oxysterols are 24-hydroxycholesterol, 25-hydroxycholesterol, and 27-hydroxycholesterol (88, 167). These oxysterols can be transported to the liver and are converted to CDCA and CA. In the brain, sterol 24-hydroxylase (CYP46A1) forms 24-hydroxycholesterol, which is converted to 7 α , 24-dihydroxycholesterol by sterol 7 α -hydroxylase (CYP39A1) in the liver. Cholesterol also can be hydroxylated at the C₂₅ position to form 25-hydroxycholesterol by sterol-25-hydroxylase, a noncytochrome P450 enzyme, followed by CYP7B1 to form 7 α , 25-dihydroxycholesterol (88). Specific to rodents, Cyp2c70 converts CDCA to α -muricholic acid (MCA) and β -MCA (185).

The classic bile acid synthesis pathway initiated by CYP7A1 accounts for the majority of bile acid synthesis (>90%) in humans (40). The alternative bile acid synthesis pathway initiated by CYP27A1 may be the predominant bile acid synthesis pathway in the neonate. After weaning, CYP7A1 is expressed, and the classic bile acid synthesis pathway dominates to synthesize bile acids. It was thought that the alternative pathway only synthesized CDCA; however, recent studies in humans and mice deficient of key genes in bile acid synthesis revealed that the alternative pathway also can synthesize CA (44). In a human patient with a *CYP7A1* gene mutation, CA and deoxycholic acid (DCA) were present in stool, indicating that the alternative pathway also produces CA (154). In mice, the classic and alternative bile acid synthesis pathways may contribute equally to produce a bile acid pool containing nearly equal amounts of T-CA and T-MCAs (derived from CDCA). In *Cyp7a1* deficient mice, the bile acid pool size decreases, and

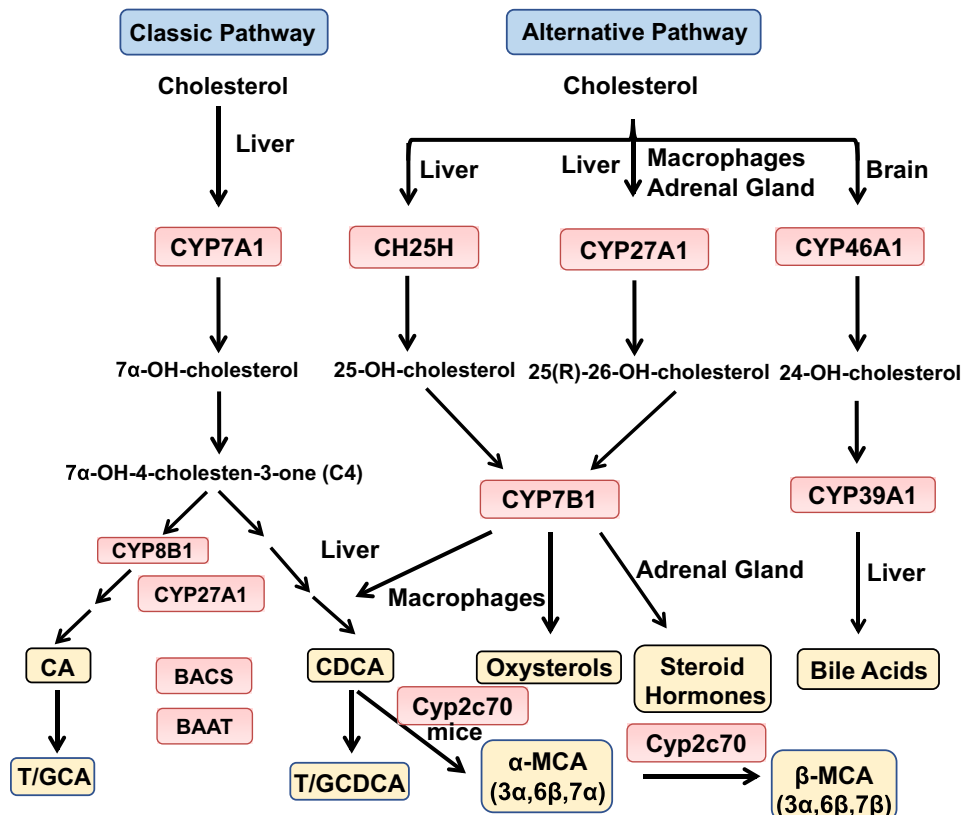


Fig. 1. Bile acid synthesis in the liver. The classic bile acid synthesis pathway is initiated by cholesterol 7 α -hydroxylase (CYP7A1). Sterol 12 α -hydroxylase (CYP8B1) is involved in synthesis of cholic acid (CA), and mitochondrial sterol 27-hydroxylase (CYP27A1) catalyzes steroid side-chain oxidation. CA and chenodeoxycholic acid (CDCA) are the two major primary bile acids synthesized in the human liver. Bile acid-CoA synthase (BACS) catalyzes the addition of a CoA group and then bile acid-CoA-to-amino acid transferase (BAAT) adds taurine (T) or glycine (G) to form T/G-conjugated bile acids for secretion in bile. The alternative bile acid synthesis pathway is initiated by hydroxylation of the steroid side chain, followed by steroid ring modifications. In the liver, cholesterol is hydroxylated by sterol 25-hydroxylase and CYP27A1 to form 25-hydroxycholesterol and 27-hydroxycholesterol [also named 25(R)-26-hydroxycholesterol], respectively, which are then hydroxylated at the 7 α -position by oxysterol 7 α -hydroxylase (CYP7B1). CYP27A1 and CYP7B1 are widely expressed in macrophages, adrenal glands, and other tissues. In the brain, sterol 24-hydroxylase (CYP46A1) converts cholesterol to 24-hydroxycholesterol, which is 7 α -hydroxylated by sterol 7 α -hydroxylase (CYP39A1) in the liver. In mice, CDCA is converted to α -muricholic acid (MCA) and β -MCA by Cyp2c70.

bile acid synthesis switches to the alternative pathway to produce more MCA, but CA still accounts for ~32% of total bile acids in the bile (44). In *Cyp7b1*-deficient mice, bile acid pool size, serum cholesterol, and triglycerides are maintained, but 25 and 27-hydrocholesterol levels are increased compared with those in wild-type mice (114). *Cyp8b1*-deficient mice have increased *Cyp7a1* expression and bile acid pool size and are resistant to Western diet-induced obesity and steatosis (8, 21, 91, 134). In *Cyp27a1*-deficient mice, *Cyp7a1* expression is induced, but bile acid pool size is reduced by ~50%, and increased cholesterol and fatty acid synthesis contribute to hepatomegaly and hypertriglyceridemia (159). Interestingly, double deficiency of *Cyp7a1* and *Cyp27a1* in mouse livers resulted in reduced bile acid pool but unaltered bile acid composition in the liver, serum, gallbladder, and intestine (164). Overexpression of *Cyp7a1* in mice enlarged the bile acid pool and protected mice from Western high-fat diet-induced obesity and insulin resistance while maintaining cholesterol homeostasis (111, 112). Thus, the classic and alternative bile acid synthesis pathways can compensate each other to produce bile acids and alter bile acid composition and pool size but still maintain bile acid and cholesterol homeostasis.

CYP27A1 is highly expressed in macrophages and metabolizes cholesterol to 27-hydroxycholesterol, which has been shown to activate liver X receptor α (LXR α) (53). 27-hydroxycholesterol is a selective-estrogen receptor modulator (193). Activation of estrogen receptor and LXR α by 27-hydroxycholesterol promoted estrogen receptor-dependent growth and LXR-dependent metastasis in a mouse model of breast cancer (126). CYP7B1 catalyzes 7 α -hydroxylation of 25-hydroxycholesterol and 27-hydroxycholesterol to convert oxysterols to bile acids in hepatocytes. A 10-wk-old boy with mutation of the *CYP7B1* gene presented with severe neonatal cholestasis, cirrhosis, and liver failure, suggesting a critical role for CYP7B1 in the regulation of oxysterol metabolism in extrahepatic tissues and macrophages as well as the importance of the alter-

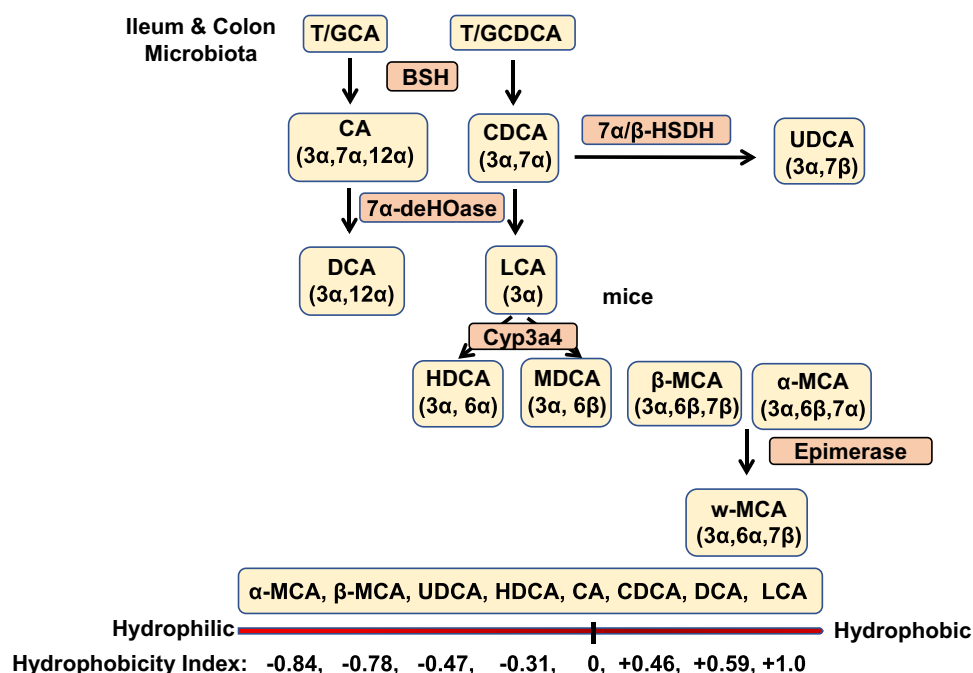
native pathway for detoxification of oxysterols and synthesis of bile acids in newborns (88). It was thought that the classic pathway is highly regulated, whereas the alternative pathway is constitutively active. More recent studies show that the alternative pathway can be regulated by steroidogenic acute regulatory protein D1-mediated transport of cholesterol to mitochondria, which lack cholesterol. Transport of cholesterol into mitochondria for 27-hydroxylation by CYP27A1 is the rate-limiting step for the alternative pathway (157). These studies support the theory that the alternative pathway plays a key role in anti-inflammation and lipogenesis. Interestingly, a recent study in mice reported that cholesterol synthesis is increased and *Cyp7b1* is induced to convert cholesterol to bile acids as an adaptive response to thermogenesis (206). Thus, the alternative pathway can be induced to produce bile acids for the promotion of energy metabolism in brown adipose tissues.

Bile Acid Transformation in the Gut

Bile acids stored in the gallbladder are secreted into the intestinal tract after each meal and are reabsorbed in the ileum. In the colon, a portion of T/G-CA and T/G-CDCA is deconjugated to CA and CDCA by bacterial bile salt hydrolase (BSH); then, bacterial 7 α -dehydroxylase removes a 7 α -hydroxyl group from CA and CDCA to form the secondary bile acids deoxycholic acid (DCA) and lithocholic acid (LCA), respectively (Fig. 2).

DCA is reabsorbed into the colon and is reconstituted and secreted into blood circulation (20%–25% of the bile acid pool), whereas LCA is circulated to the liver, reconstituted, and sulfated for excretion into urine. Human gut bacterial 3 α , 7 α , and 12 α -hydroxysteroid dehydrogenases (HSDHs) epimerize the α -hydroxyl groups of bile acids to carbonyl groups to form 3-oxo, 7-oxo, and 12-oxo-bile acids, respectively. Then, the carbonyl groups in oxo-bile acids are converted to β epimers, iso-bile acids, and epi-bile acids by 3 β , 7 β , and 12 β -HSDHs.

Fig. 2. Bile acid transformation in the gut. The primary bile acids are transformed to secondary bile acids by gut bacteria. Bile salt hydrolase (BSH) deconjugates glycine (G)/taurine (T)-conjugated bile acids, then bacterial 7 α -dehydroxylase removes a 7 α -HO group from cholic acid (CA) and chenodeoxycholic acid (CDCA) to form deoxycholic acid (DCA) and lithocholic acid (LCA), respectively. CDCA is converted to ursodeoxycholic acid (UDCA) by 7 β -hydroxysteroid dehydrogenase (7 β HSDH). UDCA can be converted to LCA by 7 β -dehydroxylase. In mouse liver, CDCA and UDCA are converted to α -muricholic acid (MCA) and β -MCA by Cyp2c70, and β -MCA is converted to ω -MCA by 6 β -epimerase by the gut bacteria. CDCA also can be converted to hyocholic acid by 7 α -epimerase in human and pig livers. In mice, LCA can be hydroxylated to hyodeoxycholic acid (HDCA) and murideoxycholic acid (MDCA). DCA and LCA can be rehydroxylated to CA and CDCA, respectively, in mouse liver. Bile acid hydrophobicity index is shown at the bottom.



The 7 α -hydroxy-bile acids have higher bactericidal activity than oxo-bile acids and β -epimers. In humans, 7 β -HSDH epimerizes the 7 α -hydroxyl group of CDCA to a 7 β -HO group, forming ursodeoxycholic acid (UDCA), increasing the solubility and decreasing the toxicity of the bile acid pool. Mouse α -MCA and β -MCA are epimerized to ω -MCA in the gut, further increasing solubility for portal circulation or fecal excretion. In humans and pigs, CDCA can be converted to the more hydrophilic hyocholic acid by 6 α -hydroxylase in the liver. In rodents, LCA can be 6 α or 6 β -hydroxylated to hyodeoxycholic acid, and murideoxycholic acid, respectively, by Cyp3a4 (Fig. 2). It is noteworthy that mice, but not humans, can rehydroxylate DCA and LCA to CA and CDCA, respectively, in the liver by a recently identified enzyme Cyp2a12 (73). Thus, in mice, most bile acids are CA (50%) and MCAs (50%), with very little DCA and CDCA, whereas in humans, CA (40%), CDCA (40%) and DCA (20%) are the major bile acids in the bile acid pool. The number of HO groups, the location of the HO groups on the steroid ring (C₆ or C₇), and stereo-configuration (α - or β -epimer) determine the hydrophobic and hydrophilic properties of bile acids. In general, 7 β - and 6 β -hydroxy-bile acids are more soluble than their respective 7 α - and 6 α -hydroxy-bile acids (Fig. 2). Bile acid hydrophobicity is determined by the order of their retention in liquid chromatography. The hydrophobicity index of CA is designated 0, and CA is more hydrophilic than CDCA (+0.46), DCA (+0.59), and LCA (+1.0), the most hydrophobic bile acid. α -MCA (−0.84) and β -MCA (−0.78) are more hydrophilic than UDCA (−0.47), hyodeoxycholic acid (−0.31) and CA (Fig. 2).

Bile Acid Pool Size and Composition

Bile acid pool size and bile acid composition are maintained by bile acid feedback regulation via the gut-to-liver axis (23, 27, 47). Alteration of the bile acid pool size and/or composition may indicate impairment in bile acid synthesis because of liver injury, obstruction of bile ducts, or inflammation. Bile acid pool size comprises the total bile acid content in the liver, serum, intestine, and gallbladder. Bile acid pool size and composition vary during fasting and postprandial states, and composition varies in serum, liver, gallbladder (bile), intestine (ileum and colon), and feces. Bile acid composition in the liver and gallbladder most closely represent the newly synthesized bile acids and recirculated bile acids in the pool. Most bile acids in the liver and gallbladder are taurine-conjugated (95%) in mice. The bile acid pool in many mammalian species, such as mice, rats, and dogs, contains predominantly taurine conjugates, whereas the bile acid pool in humans, hamsters, and rabbits contains about two-thirds glycine conjugates and one-third taurine conjugates (72). Taurine-conjugated bile acids are less toxic than their corresponding glycine-conjugated and unconjugated bile acids. The species-dependent preference for using glycine or taurine for bile acid conjugation may be due to substrate specificity of BAAT and the availability of taurine and glycine.

Most serum bile acids are unconjugated CA, DCA, and MCAs in mice and CA, DCA, and CDCA in humans. The ileum contains more conjugated bile acids than unconjugated bile acids, whereas in the colon and feces the predominant bile acid (>95%) is unconjugated DCA (95%) in mice and humans.

Increased bile acid pool size may not always imply increased synthesis, as increased intestinal absorption or decreased fecal excretion can also increase the pool size. Decreased bile acid pool size can result from reduced bile acid synthesis or biliary secretion, and/or reduced intestinal bile acid reabsorption or increased fecal bile acid secretion. During cholestasis, bile acids accumulate in hepatocytes, and biliary bile acid secretion is reduced, resulting in reduced total bile acid pool size.

BILE ACID SIGNALING IN BILE ACID HOMEOSTASIS

Bile acids activate FXR, which plays a central role in the regulation of bile acid synthesis and the enterohepatic circulation of bile acids to maintain bile acid homeostasis (reviewed in Ref. 108). FXR is highly expressed in the gastrointestinal tract and acts as a bile acid sensor to mediate bile acid feedback inhibition of bile acid synthesis and maintain very low levels of bile acids in hepatocytes to prevent liver injury and cholestasis. Bile acids differ widely in their efficacy in activation of FXR: among bile acids, CDCA is the most potent endogenous FXR agonist, whereas CA is a weak FXR agonist (200).

FXR Regulation of Bile Acid Synthesis

Two FXR-dependent pathways have been proposed to mediate bile acid feedback inhibition of bile acid synthesis (Fig. 3). Activation of FXR by bile acids induces the negative nuclear receptor small heterodimer partner (SHP) to inhibit transcription of the *Cyp7a1* and *Cyp8b1* genes in hepatocytes (24, 36, 65, 168, 219). In 1995, Pandak et al. (131) reported that intraduodenal transfusion of taurocholate inhibited *Cyp7a1* enzyme activity and mRNA in biliary-diverted rats, but an intravenous infusion did not, suggesting that TCA might induce an intestinal factor in the ileum to regulate bile acid synthesis in the liver. Ten years later, fibroblast growth factor 15 (FGF15) was identified as an intestinal FXR-regulated hormone that activates hepatic membrane FGF receptor 4 (FGFR4)/ β -Klotho complex to inhibit *Cyp7a1* and *Cyp8b1* gene transcription via activation of cJun of the mitogen-activated protein kinase (MAPK) pathway (77). FGF15-deficient mice have increased *Cyp7a1* mRNA and protein levels, supporting the notion that the gut-to-liver axis plays a critical role in bile acid feedback regulation. FGF15 is expressed in mouse intestines but is not detected in mouse serum and is not expressed in mouse liver (51, 90), whereas the human ortholog fibroblast growth factor 19 (FGF19) can be detected in human serum and hepatocytes. In human primary hepatocytes, bile acids induce FGF19 to activate extracellular signal-regulated kinase 1/2 (ERK1/2) of the MAPK pathway and inhibit *CYP7A1* gene transcription without involving SHP (180) (Fig. 3). In human ileal explants, bile acids strongly induced FGF19 transcript and protein expression (217). FGF19 levels are increased in patients with extrahepatic cholestasis and are correlated to reduced *CYP7A1* mRNA levels in human hepatocytes (170). Another study reports that variations in the *DIET1* gene may influence FGF19 levels in patients with bile acid diarrhea (101). The *Diet1* locus was identified in B6By mice, which are resistant to diet-induced hypercholesterolemia and atherosclerosis (143). Diet1 is expressed in the enterocytes, and its expression levels parallel FGF15, indicating that Diet1 may regulate bile acid synthesis by an unknown mechanism (196). It has been reported that hepatic FXR/SHP preferentially

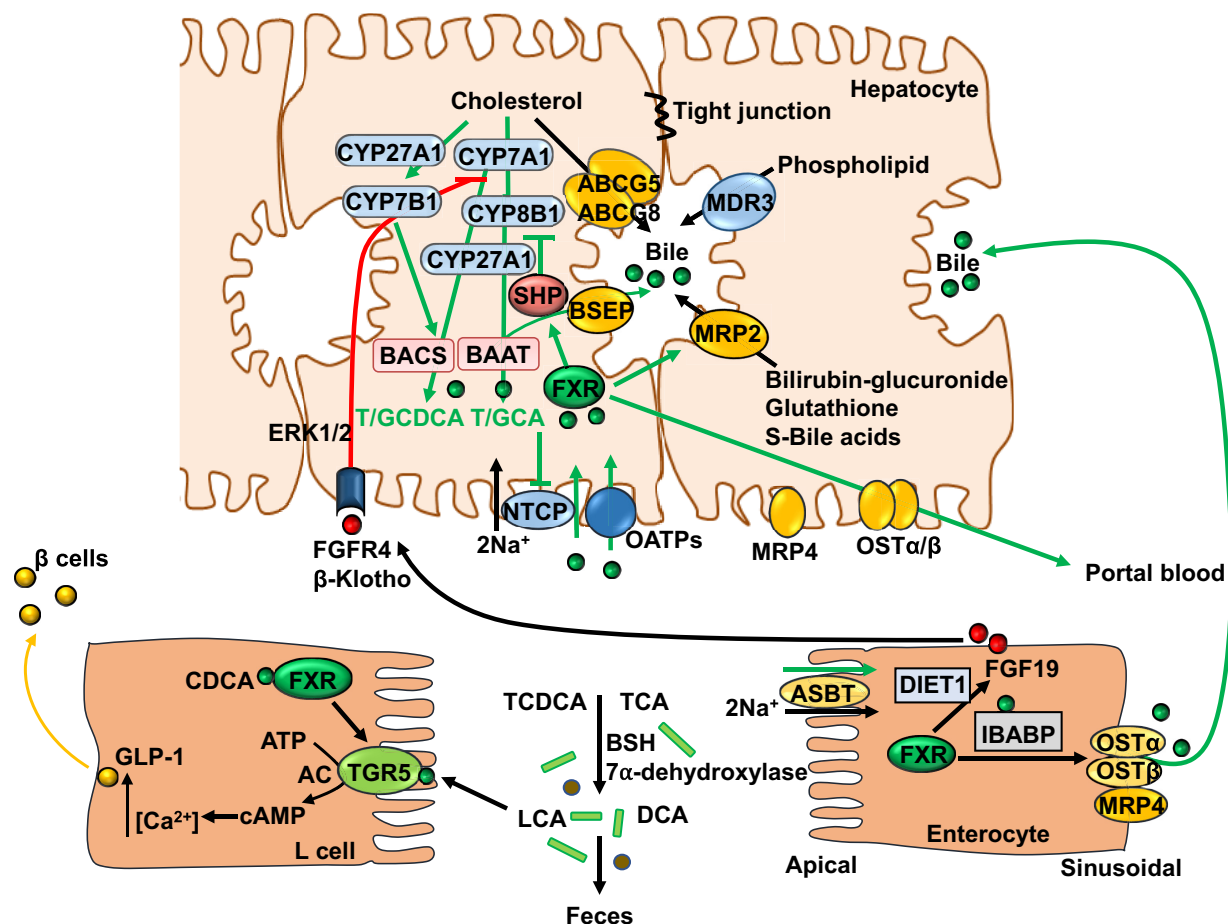


Fig. 3. Farnesoid X receptor (FXR) regulation of bile acid homeostasis. In hepatocytes, activation of FXR induces small heterodimer partner (SHP) to inhibit cholesterol 7 α -hydroxylase (CYP7A1) and sterol 12 α -hydroxylase (CYP8B1) gene transcription. FXR induces bile salt export pump (BSEP) to efflux bile acids into bile. ATP-binding cassette (ABC) G5/ABCG8 heterodimer effluxes cholesterol, whereas multidrug resistant (MDR) 3 effluxes phospholipids into bile. Bile acids, cholesterol, and phospholipids form mixed micelles. In the intestinal lumen, gut bacterial bile salt hydrolase (BSH) deconjugates taurine (T)/glycine (G) chenodeoxycholic acid (CDCA) and T/G cholic acid (CA) and bacterial 7 α -dehydroxylase removes a 7 α -HO group to form deoxycholic acid (DCA) and lithocholic acid (LCA), respectively. Bile acids are reabsorbed into enterocytes via apical sodium-dependent bile acid transporter (ASBT), which is inhibited by bile acids. In enterocytes, FXR induces ileum bile acid binding protein (IBABP) and organic solute transporter heterodimer (OST) α and OST β to efflux bile acids into portal blood circulation. DIET1 is coexpressed with FGF15 in enterocytes and modulates FGF15 levels, bile acid secretion, and bile acid pool size. FXR also induces FGF19, which binds to hepatic FGF receptor (FGFR) 4/ β -Klotho complex to activate ERK1/2 and inhibit CYP7A1 gene transcription. FXR and Takeda G protein-coupled receptor 5 (TGR5) are coexpressed in enteroendocrine L cells; FXR induces TGR5 to activate cAMP and intracellular Ca²⁺ to secrete glucagon-like peptide-1 (GLP-1), which stimulates insulin secretion from pancreatic β cells. AC, adenylyl cyclase; BAAT, bile acid-CoA-to-amino acid transferase; BACS, bile salt CoA-synthase; CYP27A1, sterol 27-hydroxylase; CYP7B1, oxysterol 7 α -hydroxylase; MRP, MDR-related protein; NTCP, sodium/taurocholate cotransporting polypeptide.

inhibits *Cyp8b1* gene, whereas intestinal FGF15/liver FGFR4 signaling preferentially inhibits *Cyp7a1* gene transcription (97). Bile acid concentration is much higher in the ileum and colon (in millimolars) than that in the liver (in micromolars). It is likely that bile acid activation of intestinal FXR/FGF19 signaling to activate the hepatic FGFR4 pathway is the major physiological mechanism for bile acid feedback regulation of bile acid synthesis. When bile acid concentrations increase in the liver during cholestasis, the FXR/SHP pathway may be activated to inhibit bile acid synthesis and prevent bile acid reabsorption from portal blood. In addition, bile acids induce the proinflammatory cytokines TNF α and IL-1 β in macrophages/Kupffer cells to activate Toll-like receptor 4 in hepatocytes and inhibit CYP7A1 and CYP8B1 via ERK1/2/JNK signaling (116). Furthermore, post-transcriptional regulation of CYP7A1 mRNA stability may also regulate CYP7A1 expres-

sion. The liver expresses multiple CYP7A1 mRNA species with difference lengths of the 3' untranslated region, which contains multiple AUUU sequence motifs for the destabilization of mRNA (113). A recent study reports that activation of FXR induces an RNA binding protein ZFP36L1, which binds to the 3' untranslated region to destabilize CYP7A1 mRNA (188).

FXR Regulation of Bile Acid Homeostasis

FXR plays a key role in the regulation of bile acid enterohepatic circulation and transport from liver to intestine (Fig. 3). In hepatocytes, FXR induces expression of bile salt export pump (BSEP) (ATP-binding cassette transporter B11), which effluxes bile acids into bile. FXR also induces ATP-binding cassette transporter (ABC) G5 and ABCG8 to efflux choles-

terol and multidrug resistant transporter 3 (MDR3 or ABCB4) to efflux phospholipids into bile. MDR-related protein 2 (MRP2 or ABCC2) effluxes bilirubin, glutathione, glucuronate, and sulfate conjugates of bile acids into bile. Bile acids, cholesterol, and phospholipids form mixed micelles to concentrate bile acids and to prevent cholesterol precipitation in the gallbladder bile. On the sinusoidal membrane, bile acids inhibit sodium/taurocholate cotransporting polypeptide (NTCP) and organic anion transporting peptides. Thus, FXR acts as a bile acid sensor to maintain low intrahepatic bile acid concentration and to prevent cholestatic liver injury. In the ileum, bile acids are efficiently reabsorbed into enterocytes via apical sodium-dependent bile acid transporter (SLC10A2). FXR inhibits apical sodium-dependent bile acid transporter but induces ileum bile acid binding protein, which binds and transports bile acids across enterocytes to the sinusoidal membrane, where FXR induces organic solute transporter α and β heterodimer (OST α and OST β , respectively) (SLC51A and SLC51B) and MRP4 to secrete bile acids into portal circulation (Fig. 3). OST α , OST β , and MRP4 are also expressed in the sinusoidal membrane of hepatocytes to secrete bile acids into portal blood. Thus, FXR also acts as a sensor to control bile acid reabsorption and secretion in portal blood to prevent accumulation of bile acids in enterocytes and protect intestinal barrier function. Portal circulation of bile acids from intestine to hepatocytes, in which sinusoidal sodium/taurocholate cotransporting polypeptide reabsorbs bile acids from portal blood, completes the enterohepatic circulation of bile acids.

BILE ACID SIGNALING IN METABOLIC REGULATION

Bile Acids in the Gut-Liver-Brain Axis and Circadian Rhythms

Figure 4 illustrates the central role of bile acids in the gut-liver-brain axis to regulate metabolic homeostasis. The enterohepatic circulation of bile acids maintains the bile acid pool. In the liver, bile acids regulate lipid, glucose, and cholesterol metabolism, whereas in the gastrointestinal tract, bile acids control bacterial overgrowth, and gut bacteria regulate bile acid metabolism to control bile acid composition and pool size (45).

Circadian rhythms refer to physiological processes that occur with a repeating period of ~24 h. Circadian rhythms are generated and maintained by the suprachiasmatic nucleus (SCN), located in the hypothalamus, and ensure that internal physiology is appropriately synchronized to the external environment. In the SCN, protein products of the core clock genes *Clock* and *Bmal1* heterodimerize and induce the transcription of additional clock genes *Period* (*Per*) and *Cryptochrome* (*Cry*). *Per* and *Cry* proteins feed back to negatively regulate *Clock* and *BMAL1* proteins, and the *Per/Cry* complex is eventually phosphorylated by casein kinase, marking it for degradation. The nuclear receptors *Rev-erb α* and retinoic acid receptor-related orphan receptor α participate in an accessory feedback loop to further regulate *Bmal1* transcription. These feedback loops take ~24 h to complete and are synchronized by daily retinal photic input signals. The SCN also directs the neural and hormonal signals that synchronize the peripheral clocks that exist in nearly all tissues (45).

In the liver, rhythms are synchronized or altered by hormones, fasting and feeding, and diet (27, 46). *Clock* and *Bmal1* regulate the clock-controlled gene D-site binding protein,

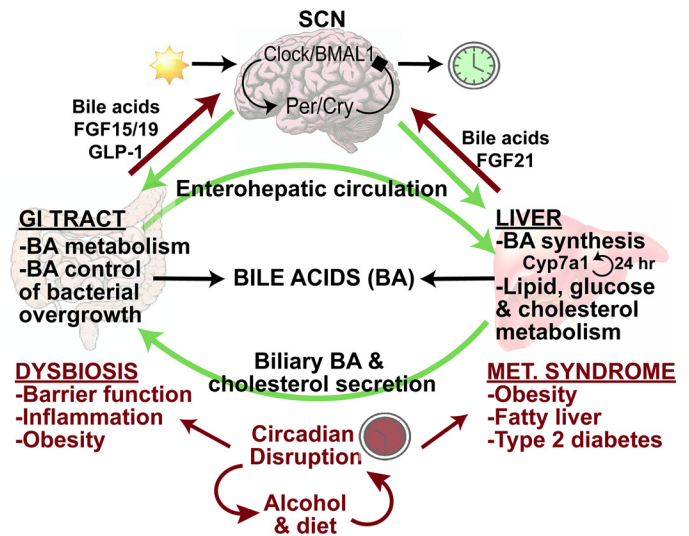


Fig. 4. Bile acids (BAs) in the gut-liver-brain axis and circadian rhythms. Circadian rhythms are generated and maintained by the suprachiasmatic nucleus (SCN) via rhythmic transcription and translation of core clock genes. *Clock* and *Bmal1* induce *Period* (*Per*) and *Cryptochrome* (*Cry*), which feed back to inhibit *Clock/Bmal1*. All peripheral organs have molecular clocks that are synchronized to the SCN to regulate rhythms in lipid, glucose, and cholesterol metabolism, as well as cholesterol 7 α -hydroxylase (*CYP7A1*) expression in the liver. In the gastrointestinal (GI) tract, gut bacteria metabolize bile acids, which control bacterial overgrowth. Dysbiosis, caused by circadian disruption, alcohol, or high-fat diets, impairs intestinal barrier function and causes inflammation. Dysbiosis also contributes to obesity, fatty liver, and type 2 diabetes mellitus. In the gut-to-brain axis, glucagon-like peptide-1 (GLP-1), FGF19, and bile acids mediate signaling cross-talk between the gut and brain, and FGF21 and bile acids mediate signaling cross-talk between the brain and liver.

whereas *Rev-erb α* regulates the transcription of the bile acid synthesis genes *Cyp7a1* and *Cyp8b1*, the gluconeogenesis genes phosphoenolpyruvate kinase and glucose-6-phosphatase, and the lipid metabolism genes sterol regulatory element binding protein 1c (*Srebp1c*), fatty acid synthase, and acetyl-CoA carboxylase.

Bile acid synthesis exhibits a distinct diurnal rhythm, peaking at night and reaching a nadir at midday in mice (45). There are few studies on rhythms in bile acid synthesis in humans. In one study, bile acid synthesis (assayed by serum C4) showed two peaks, at 1:00 PM and 9:00 PM, declining at night and returning to the baseline the next morning (56). The postprandial rise of bile acid synthesis corresponds to the timing of food intake and is regulated by FGF19, which precedes the decline in bile acid synthesis (57, 117). Dysregulation of bile acid synthesis affects triglyceride and cholesterol homeostasis and contributes to obesity, fatty liver disease, type 2 diabetes, and metabolic syndrome, which is a collection of five metabolic phenotypes: hyperglycemia, hyperlipidemia, hypertension, insulin resistance, and obesity. Circadian disruption, diet, or alcohol drinking can cause dysbiosis (alteration of the gut microbiota that negatively impacts host health), impaired intestinal barrier function (leaky gut), inflammatory bowel diseases, fatty liver disease, diabetes, and obesity. Bile acids and circulating FGF19 levels vary widely in humans (56, 117). Bile acid synthesis is reduced in women compared with men and is correlated to serum triglyceride levels (57). Interestingly, a recent study of healthy men showed asynchronous rhythms of circulating conjugated and unconjugated bile acids (2). Bile

acid synthesis is predominant in the daytime, whereas cholesterol is synthesized at night. Serum-conjugated bile acids peak after food intake, and the subsequent increase of FGF19 reduces bile acid synthesis and conjugated bile acids. Unconjugated bile acids exhibit one peak from night to early morning and are not rhythmic.

Circulating fibroblast growth factor 21 (FGF21) varies greatly in healthy individuals, with no correlation to age, gender, body mass index, serum lipid levels, or glucose levels (58). Increased free fatty acids during fasting activate peroxisome proliferator-activated receptor (PPAR) α and PPAR γ coactivator protein-1 α (PGC-1 α) to stimulate FGF21 production in the liver and adipose tissue. As an adaptation to prolonged fasting, increased FGF21 stimulates glucose and energy metabolism in mice to maintain metabolic homeostasis, independent of insulin (78, 150). FGF21 reduces serum triglycerides by stimulating energy metabolism in adipose tissue (172) and inhibits mouse mammalian target of rapamycin complex 1 (mTORC1) signaling to improve insulin sensitivity and reduce hepatic steatosis (63, 211). FGF21 induces PGC-1 α to stimulate fatty acid oxidation, ketogenesis, and energy metabolism during adaptive starvation (150), and in the brain, regulates circadian behavior, physical activity, and nutrient preference for carbohydrates, fats, and protein, and it reduces sweet and alcohol preference in mice (10, 186).

Bile Acid Regulation of Lipid Metabolism and Inflammation

Activation of FXR has been shown to improve glucose and lipid metabolism and reduce inflammation in diabetes (54, 64, 108, 153, 190). The role and mechanism of bile acid signaling in lipid lowering and glycemic control are not completely understood. Deficiency of *Fxr* in mice increased hepatic triglycerides, serum triglycerides, and cholesterol and promoted a proatherogenic lipid profile, suggesting that FXR regulates lipid and lipoprotein metabolism (178). Activation of mouse FXR inhibits SREBP-1c-mediated lipogenesis via induction of the FXR-SHP pathway, inhibiting LXR induction of SREBP-1c and the lipogenic genes fatty acid synthase, acetyl-CoA carboxylase, and stearoyl-CoA desaturase-1 (204). FXR activation also inhibits glucose-induced carbohydrate response element binding protein, which regulates glycolysis genes (17). However, in mice, transgenic overexpression of *Cyp7a1* increased the bile acid pool, increased T-CDCA, and reduced T-MCAs, indicating activation of hepatic FXR signaling although none of the FXR target genes in lipogenesis were repressed (112). These mice were resistant to diet-induced obesity and diabetes. Interestingly, *Cyp7a1*-transgenic mice have increased cholesterol synthesis, but bile acid and cholesterol homeostasis were maintained by increasing biliary secretion of bile acids, cholesterol, and lipids (109). These studies showed that increasing bile acid synthesis stimulated SREBP-2-mediated cholesterol synthesis and reduced SREBP-1c-mediated lipogenesis by shunting acetyl-CoA from lipogenesis to cholesterol synthesis, resulting in reduced lipogenesis. FXR has been shown to induce human peroxisome proliferator-activated receptor α (PPAR α), which stimulates fatty acid oxidation (145). Activation of FXR induces apolipoprotein (Apo) CII and ApoA5 but inhibits ApoA1 and ApoCIII, ultimately activating lipoprotein lipase in VLDL particles to reduce serum triglycerides (29). Free fatty acids mobilized from adipose

tissue during fasting and starvation are transported to hepatocytes for synthesis of triglycerides, which are assembled in VLDL particles for secretion, transport, and distribution to muscle and other tissues for energy metabolism. Increased hepatic free fatty acid metabolism and VLDL secretion can cause lipotoxicity and induce endoplasmic reticulum (ER) stress and reactive oxidizing species (ROS).

The effects of bile acids on energy metabolism may be mainly due to activation of TGR5 by secondary bile acids (T/LCA and T/DCA). TGR5 is widely expressed in the epithelial cells of the intestine, gallbladder, and liver sinusoid, and in the Kupffer cells but not in hepatocytes. TGR5 activates adenylyl cyclase (AC) to convert ATP to cAMP, which induces protein kinase A to activate cAMP response element binding protein (CREB), which is involved in various cAMP signaling pathways. In muscle and brown adipose tissues, TGR5 induces deiodinase type 2 (DIO2), which converts thyroid hormone thyroxine to 3,5,3'-triiodothyronine and stimulates energy metabolism in the mitochondria (203). TGR5 also promotes adipose tissue browning, induces uncoupling proteins, and activates PPAR α and PGC-1 α to increase mitochondrial oxidative phosphorylation and energy metabolism and to prevent obesity and diabetes (50, 141, 148, 183). In the mouse intestine, activation of TGR5 stimulates glucagon-like peptide-1 (GLP-1) secretion from intestinal enteroendocrine L cells to increase insulin secretion from pancreatic β -cells and to increase glucose tolerance (Fig. 3) (189). TGR5 is also anti-inflammatory via inhibition of NF- κ B-mediated proinflammatory cytokine production (202), induction of nitric oxide (NO) production to reduce monocyte adhesion in vascular endothelial cells (93), induction of endothelial NO synthase (eNOS) in liver sinusoidal endothelial cells (92), and inhibition of atherosclerosis by reducing macrophage inflammation and lipid loading (147).

Bile Acid Regulation of Glucose Metabolism

Upon feeding, bile acids are secreted from the gallbladder, and hepatic bile acid synthesis is derepressed. In the postprandial state, bile acids stimulate insulin signaling and improve glucose metabolism. In the late postprandial state, bile acids activate FXR to induce FGF19, which stimulates glycogen synthesis and lowers fasting plasma glucose independent of insulin (96). FGF15/19 also inhibits hepatic gluconeogenic gene expression by inhibiting the CREB-PGC-1 α pathway (149). An early study reported that FXR bound to and activated the promoter of phosphoenolpyruvate carboxykinase (PEPCK), and FXR agonism induced PEPCK mRNA and glucose output in human and rat hepatocytes and mouse liver (181). In contrast, a later study reported that bile acid activation of FXR inhibited gluconeogenic gene expression by inducing SHP, which inhibits hepatocyte nuclear factor 4 α and forkhead box O1 activation of PEPCK and reduces serum glucose in wild-type mice. SHP also inhibits growth hormone-mediated induction of gluconeogenesis by inhibiting signal transducer and activator of transcription 5 signaling (95). *Fxr*^{-/-} mice developed fatty liver disease, had elevated serum free fatty acids and glucose, and were insulin resistant and hyperglycemic (118). Furthermore, FXR agonism improved hyperglycemia, enhanced insulin signaling in adipocytes, and improved insulin resistance in *ob/ob* and *db/db* mice (16, 220). In

complete contrast, it was reported later that whole body *Fxr*-deficient mice had improved glucose homeostasis and adipose tissue insulin sensitivity, whereas hepatic insulin sensitivity did not change, and hepatic steatosis was aggravated (153). Further, this study showed that liver-specific *Fxr*^{-/-} mice were not protected from diet-induced obesity and insulin resistance, suggesting FXR-independent regulation of glucose metabolism and obesity (153). It has been reported that both FXR and TGR5 are expressed in pancreatic β cells, and bile acid signaling through these two receptors may directly regulate insulin synthesis, secretion and sensitivity, and glucose metabolism (41, 99, 158, 171, 189).

INTESTINAL FXR IN LIVER METABOLISM

The implication of intestinal FXR in liver metabolism was first reported by Sayin et al. (169) in their study of germ-free mice and *Fxr*^{-/-} mice and by Li et al. (105) in the study of intestine-specific-*Fxr*^{-/-} mice. Analysis of bile acid composition revealed that T-MCA levels and bile acid pool size were reduced in conventionally raised mice compared with germ-free mice (169). This study identified T- α MCA and T- β MCA as intestinal FXR antagonists and confirmed the role of the gut microbiota in FXR-mediated inhibition of bile acid synthesis. High-fat diet-fed mice treated with tempol, an antioxidant, had reduced *Lactobacillus* and BSH activity to increase T β -MCA, which antagonized intestinal FXR, reduced FGF15, and derepressed bile acid synthesis to improve diet-induced obesity (DIO) and diabetes (105). Furthermore, they showed that intestine-specific-*Fxr*^{-/-} mice were resistant to DIO, indicating that intestinal FXR signaling plays a critical role in the modulation of metabolic disease (80, 81). These studies also discovered that intestinal FXR induces ceramide synthesis and increases serum and liver ceramide concentrations (209). Ceramides cause ER stress and mitochondrial oxidative stress and inhibit insulin signaling in hepatocytes (64). Paradoxically, the intestine-selective FXR agonist fexaramine altered serum bile acid composition, promoted adipose tissue browning, and also reduced DIO in mice (43). It was shown that fexaramine treatment altered the gut microbiota by increasing the abundance of the LCA-producing gut bacteria *Acetatifactor* and *Bacteroides* (135). These bacteria have both 7 α and 7 β -dehydroxylase activity to convert CDCA and UDCA to LCA. LCA and DCA activate TGR5 to stimulate GLP-1 secretion from L cells and improve insulin sensitivity. TGR5 activation also promotes adipose tissue browning and energy metabolism to reduce weight in obese diabetic mice (135). These studies demonstrate that intestinal bile acid-FXR signaling plays a critical role in the regulation of liver metabolism.

FXR and TGR5 Signal Cross-talk in Enteroendocrine Cells

FXR and TGR5 are colocalized in enteroendocrine L cells (Fig. 3). Activation of FXR has been shown to induce *Tgr5* gene transcription via an FXR binding site located in the *Tgr5* gene promoter (138). LCA and DCA levels are high in the colon to activate enteroendocrine TGR5. Glucose is transported into L cells via sodium glucose transporter 1 and produces cAMP from ATP, which activates CREB. CREB induces prohormone convertase 1/3 to cleave preproglucagon to GLP-1. cAMP also stimulates Ca²⁺ secretion from the mitochondria to the cytosol and inhibits the K⁺_{ATP} channel,

depolarizing the membrane potential and stimulating GLP-1 secretion from L cells (138). GLP-1 stimulates insulin secretion from pancreatic β cells to improve insulin sensitivity and promote adipose tissue browning and energy metabolism to reduce weight (Fig. 3).

BILE ACID SIGNALING IN LIVER METABOLISM DURING FASTING TO FEEDING TRANSITION

Bile acids facilitate nutrient absorption and act as nutrient sensors that regulate metabolism during fasting and feeding. Among all bile acids, cholic acid has the lowest critical micelle concentration (50 μ M) and is the most efficacious bile acid in the absorption of dietary cholesterol and fat. Fasting and feeding rapidly alter the peak expression of the *Cyp7a1* gene and the rhythmicity of bile acid synthesis, pool size and composition, and hepatic metabolism in mice (26, 45, 46) and humans (48). Feeding rapidly induces *CYP7A1* but inhibits *CYP8B1* expression, increasing bile acid synthesis and aiding in nutrient absorption during the postprandial state (Fig. 5).

Stimulating bile acid synthesis reduces hepatic cholesterol and induces hepatic autophagy via insulin/AKT signaling and inhibition of mTORC1 (201). Autophagy is a highly conserved lysosomal pathway that is programmed to maintain lipid and metabolic homeostasis and cellular function (30). mTORC1 is regulated by cellular nutrients and energy to stimulate the anabolic pathways that consume ATP and inhibit the catabolic pathways that produce energy. In the postprandial state, FXR activates insulin-AKT signaling to inhibit mTORC1/pS6P-signaling, which is known to promote nuclear translocation of SREBP-1c and lipogenesis, thus inhibiting de novo lipogenesis in the postprandial state. CDCA activates FXR in enteroendocrine L cells to induce TGR5 expression and signaling, increase intracellular cAMP and Ca²⁺, and stimulate glucose-induced GLP-1 secretion, whereas activation of TGR5 in brown adipose tissue stimulates energy metabolism.

In the late postprandial state to the postabsorptive state, intestinal FXR induces FGF19, which activates hepatic FGFR4-ERK1/2 signaling to inhibit bile acid synthesis (180). In mice, Fgf15 regulates glucose metabolism and glycogen and protein synthesis when insulin levels are decreased (96). In the mouse intestine, activation of FXR induces ceramide synthesis (209), which causes insulin resistance in nonalcoholic fatty liver disease (NAFLD) in both rodents and humans (19, 55, 64, 214) via mTORC1 signaling, SREBP-1c-mediated lipogenesis, ER stress, and ROS.

During prolonged fasting and starvation, CYP7A1 expression and bile acid synthesis is reduced, but CYP8B1 is induced to increase CA synthesis and thus increase DCA in the colon, promoting ceramide synthesis and SREBP-1c-mediated lipogenesis.

INTERACTIONS BETWEEN BILE ACIDS AND GUT MICROBIOTA

Gut Microbiota

The human gut microbiome is composed of trillions of bacteria that belong to four major phyla: Firmicutes (60%), Bacteroidetes (22%), Actinobacteria (17%) and Proteobacteria (1%) (76). Recent metagenomic studies of the human gut microbiome revealed over 15,000 genomes and genomic blue-

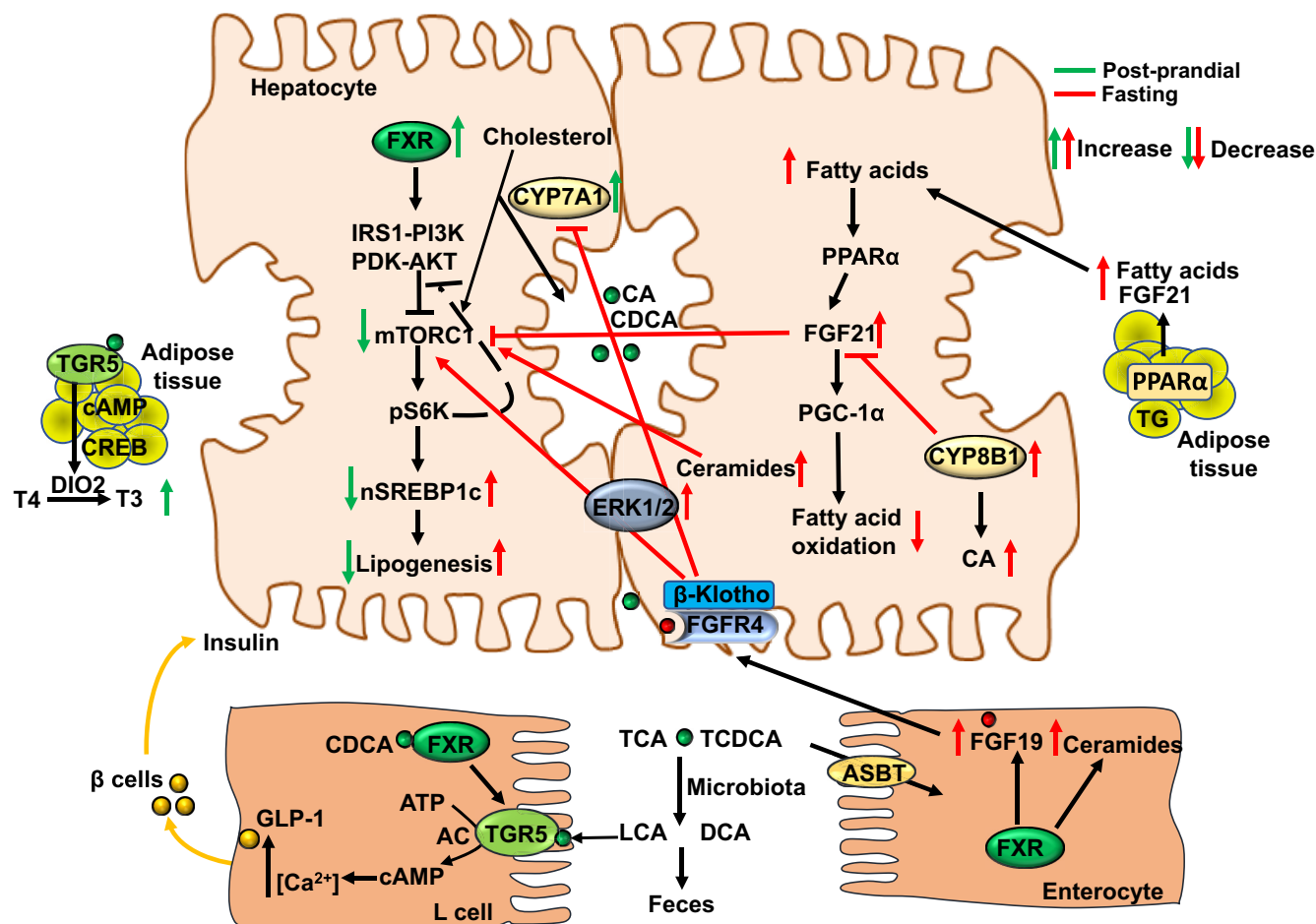


Fig. 5. Nutrient regulation of bile acid synthesis and hepatic metabolism. Feeding rapidly induces cholesterol 7 α -hydroxylase (*CYP7A1*) but inhibits sterol 12 α -hydroxylase (*CYP8B1*) expression to increase bile acid synthesis and aid in nutrient absorption during the postprandial state. Stimulating bile acid synthesis induces hepatic autophagy via insulin/AKT signaling to inhibit the mammalian target of rapamycin complex 1 (mTORC1). Farnesoid X receptor (FXR) activates insulin receptor substrate 1-AKT (protein kinase B) signaling to inhibit mTORC1/pS6K-signaling to promote nuclear translocation of sterol regulatory element binding protein 1c (nSREBP-1c) and lipogenesis. During the postprandial state, glucose is transported to enterocytes via the sodium-glucose-cotransporter 2. Chenodeoxycholic acid (CDCA) activates FXR in enteroendocrine L cells to induce Takeda G protein-coupled receptor 5 (TGR5) signaling and stimulate glucose-induced glucagon-like peptide-1 (GLP-1) secretion via increased intracellular cAMP and Ca²⁺. GLP-1 promotes insulin secretion from pancreatic β cells and increases insulin sensitivity. Activation of TGR5 in brown adipose tissue stimulates energy metabolism and the conversion of thyroxine to 3,5,3'-triiodothyronine. In the late post-prandial state to postabsorptive state, intestinal FXR induces FGF19, which activates hepatic FGF receptor (FGFR) 4-ERK1/2 signaling to inhibit bile acid synthesis. FGF19 regulates glucose metabolism, glycogen synthesis, and protein synthesis when insulin levels are decreased. In the intestine, activation of FXR induces ceramide synthesis. Ceramides activate mTORC1 signaling to induce SREBP-1c-mediated lipogenesis and induce ER stress and ROS to cause insulin resistance. During prolonged fasting or starvation, *CYP7A1* expression and bile acid synthesis is reduced, but *CYP8B1* is induced to increase cholic acid (CA) synthesis and deoxycholic acid (DCA) content in the colon, promoting ceramide synthesis and SREBP-1c-mediated lipogenesis. Increasing free fatty acids activate peroxisome proliferator-activated receptor (PPAR) α and PPAR γ coactivator protein-1 α (PGC-1 α) to stimulate FGF21 production in liver and adipose tissue. As an adaptation to prolonged fasting to maintain metabolic homeostasis, increased FGF21 stimulates glucose and energy metabolism independent of insulin. FGF21 reduces serum triglycerides by stimulating energy metabolism in adipose tissue. FGF21 also inhibits mTORC1 signaling to improve insulin sensitivity and reduce hepatic steatosis. Green arrows indicate changes in the postprandial state and red arrows indicate changes in the fasting state. ASBT, apical sodium-dependent bile acid transporter AC, adenylyl cyclase; CREB, cAMP response element binding protein; DIO2, deiodinase type 2; IRS1, insulin-resistant substrate 1; LCA, lithocholic acid; PDK, phosphoinositide-dependent kinase; PI3K, phosphoinositide 3-kinase; TG, triglycerides.

prints (4, 133). Firmicutes are butyrate-producing bacteria, whereas Bacteroidetes degrade carbohydrates. The increase in the ratio of Firmicutes to Bacteroidetes commonly seen in patients with obesity allows gut microbes to extract energy more efficiently from high-fat diets, thus increasing adiposity. Animal-based diets alter the human gut microbiota by increasing the bile-tolerant bacteria *Bilophila wadsworthia* and decreasing Firmicutes (32). High-saturated-fat diets induce TCA to increase the expansion of *Biophila wadsworthia* and promote proinflammatory responses and inflammatory bowel dis-

ease in mice (38). Gut bacterial diversity is reduced in liver diseases; patients with NASH and NAFLD have significantly higher levels of Bacteroidetes and lower Firmicutes compared with healthy control subjects (122, 175). In advanced fibrosis, Gram-negative Proteobacteria is significantly increased, suggesting that Gram-negative bacteria might contribute to liver fibrosis (115). Patients with cirrhosis have increased fecal Enterobacteriaceae (a pathobiont) but reduced Ruminococcaceae, Lachnospiraceae, and Blautia compared with control subjects (89).

The reciprocal relationship between the gut microbiota and bile acids has been recognized for over half a century. In humans, CDCA is positively correlated to Enterobacteriaceae abundance, DCA is positively correlated to Ruminococcaceae, and LCA/CDCA positively correlated to Blautia (89). DCA and LCA are strong bactericides that control gut bacterial growth and the community of gut bacteria (microbiota). Gut microbes, in turn, deconjugate primary bile acids and convert them to secondary bile acids and thus control bile acid composition and the circulating bile acid pool via intestinal FXR/Fgf15 (FGF19) signaling (169). A study of germ-free and conventionally raised wild-type and *Fxr*^{-/-} mice revealed that the gut microbiota promoted weight gain and hepatic steatosis by altering bile acid composition and reducing pool size via FXR signaling (132). In humans, a BSH-active probiotic increased bile acids and FGF19 (119). Gut bacteria harvest nutrients and energy from food ingested by the host and produce metabolites that affect host metabolism (76, 198). Diet, drugs, antibiotics, alcohol, and toxic bacterial metabolites disrupt the gut bacteria community and have negative effects on host metabolism (dysbiosis) and contribute to diseases including obesity, type 2 diabetes mellitus (T2DM), nonalcoholic fatty liver disease (NAFLD), hepatocellular carcinoma (HCC), inflammatory bowel diseases (IBDs), and atherosclerosis (28, 76, 85, 139, 144, 160, 194, 218).

Bacterial BSH and 7 α -dehydroxylase

Bacterial BSH and 7 α -dehydroxylase play critical roles in the regulation of bile acid metabolism and homeostasis, and alteration of their activity significantly impacts host metabolism and health (82, 85, 100, 161). BSH is abundantly expressed in the human gut and is expressed in a broad spectrum of bacteria such as the Gram-positive genera *Clostridium*, *Enterococcus*, *Listeria*, and *Lactobacillus* (all of which belong to the phylum Firmicutes) and the Gram-negative genus *Bacteroides*, whereas 7 α -dehydroxylase is restricted to a limited number of low abundant anaerobes (<1% of intestinal bacteria) (161). The multiple steps of 7 α -dehydroxylation are catalyzed by enzymes encoded on a cluster of bile acid-inducible (*bai*) genes (162). The majority of the *Bai*-expressing bacteria are classified in the Ruminococcaceae (90%) family. The *Bai* gene operon (*Bai A–J*) in Clostridiales has been sequenced, and the enzymes encoded by the *bai* genes were characterized. The *baiE* gene encodes bile acid 7 α -HSDH, and the *baiI* gene may encode 7 β -HSDH.

Expression of a cloned BSH enzyme in the gastrointestinal tract of mice significantly altered serum bile acid species and transcription of the key genes involved in lipid, cholesterol, and circadian metabolism and gastrointestinal homeostasis (86). Interestingly, high expression of BSH activity in conventionally raised mice significantly reduced weight gain, plasma cholesterol, and liver triglycerides. A metagenome-wide association study of the gut microbiota in patients with T2DM reported increased *Lactobacillus* abundance (156). Reducing *Lactobacillus* by the antioxidant tempol or *Bacteroides fragilis* by metformin improves DIO in mice and in patients with T2DM (105, 182). Compared with those found in healthy control subjects, Firmicutes-derived BSH and 7 α -dehydroxylase and HSDH genes are reduced in patients with ulcerative

colitis and T2DM but not in patients with Crohn's disease (100).

BILE ACID METABOLISM IN NONALCOHOLIC FATTY LIVER DISEASE

The global epidemic of obesity has increased the prevalence of T2DM, NAFLD, and cardiovascular disease. NAFLD is a significant complication of obesity and T2DM, and an independent risk factor for cardiovascular disease. NAFLD has become the most common chronic liver disease, affecting ~30% of the US population. NAFLD is a spectrum of liver diseases ranging from simple hepatic steatosis to progressive nonalcoholic steatohepatitis (NASH) with or without fibrosis and cirrhosis. Simple steatosis is reversible, but 30% of patients with NAFLD progress to NASH, which affects ~15% of the US population. NASH is a chronic liver disease with inflammation, macrovascular ballooning, macrophage infiltration, and fibrosis. NASH fibrosis can progress to cirrhosis and HCC in ~0.5% of patients with NAFLD (5, 216). HCC is the sixth most common cancer, and the rate of liver cancer death has increased rapidly, becoming the second most lethal cancer after pancreatic cancer (197). The pathogenesis and progression from simple hepatic steatosis to NASH are not completely understood. Many factors, including lipotoxicity, cigarette smoking, insulin resistance, cholesterol, and reactive oxidizing species (ROS), have been implicated in NASH progression. Patients with NASH have increased de novo lipogenesis, which causes accumulation of toxic lipids, including saturated fatty acids, lysophosphatidylcholine (LPC), free cholesterol, and ceramides, that can directly cause ER stress, apoptosis, liver inflammation, and injury (94). ER stress induces de novo lipogenesis and impaired hepatic lipid and glucose homeostasis (7).

Bile acids play a critical role in the control of metabolic disease, obesity, T2DM, and NAFLD (20). Patients with NAFLD have increased CA, CDCA, and bile acid synthesis and an increased ratio of primary bile acids to secondary bile acids (122). A more recent study reports that patients with NASH have increased circulating conjugated primary bile acids (especially G/T-CA and T-CDCA), an increased ratio of conjugated CA to CDCA, and decreased secondary bile acids (155). It is not clear whether increased and altered serum bile acids are the causes or consequences of NASH pathogenesis. In mice, it was shown that accumulation of toxic bile acids in hepatocytes can activate ER stress, de novo lipogenesis, and progression of hepatic steatosis to NASH (67, 70, 94). In patients with obesity and insulin resistance, serum 12 α -hydroxylated bile acid levels are increased (66), and insulin and glucose have been implicated in the regulation of bile acid synthesis (107, 110). Metabolic phenotypes in diabetes, hyperinsulinemia, and hyperglycemia induce *Cyp8b1* expression and increase serum cholesterol and 12 α -hydroxylated bile acids in mice (137). A recent study reported that glucose-6-phosphate induces *Cyp8b1* expression via glucose induction of carbohydrate response element binding protein (74). Increasing CA synthesis increases dietary cholesterol absorption and reduces biliary cholesterol secretion. Deficiency of *Cyp8b1* in mice increases T-MCAs, which antagonize intestinal FXR to reduce FGF15 and increase bile acid synthesis and pool size. These mice are protected from diet-induced obesity and insulin resistance, hepatic steatosis,

dyslipidemia, and atherosclerosis (21, 91, 134, 179). On the other hand, overexpression of *Cyp8b1* increases SREBP-1c-mediated lipogenesis, dyslipidemia, and insulin resistance (136).

BILE ACID METABOLISM IN ALCOHOL-ASSOCIATED LIVER DISEASE

Alcohol-associated liver disease (AALD) is a major cause of chronic liver disease, is associated with ~50% of deaths caused by liver disease, and is the primary reason for one-third of liver transplants. AALD accounts for about half of the deaths caused by liver cirrhosis (59). Alcohol is a high-calorie, high-carbohydrate substance, and chronic alcohol consumption may lead to hepatic steatosis and progress to inflammation, fibrosis, cirrhosis, and HCC. Ethanol is metabolized by alcohol dehydrogenase and CYP2E1 to acetaldehyde, which is then converted to acetate by aldehyde dehydrogenase. Acetate is a precursor for the synthesis of fatty acids and glucose. Alcohol metabolism increases the cellular NADH/NAD⁺ ratio, which inhibits fatty acid oxidation and stimulates lipogenesis (215). Ethanol metabolism generates aldehydes that produce reactive oxidizing species and promote ER stress and DNA and protein adducts, causing liver injury, intestinal barrier dysfunction, and innate immune and adaptive responses. Alcohol increases gut permeability to release bacterial endotoxins and lipopolysaccharides (LPS) from the gut lumen to the liver, activating Toll-like receptor 4 signaling and causing inflammation and liver injury in AALD (184). There are several established alcohol research models, and each model may differentially affect the gut microbiome. However, in general, alcohol increases intestinal bacteria overgrowth of endotoxin-producing Gram-negative bacteria and causes gut microbial dysbiosis, which is considered to be the major cause of AALD progression to cirrhosis. In humans, chronic alcohol consumption was associated with long-term changes in colonic bacterial composition (125).

Active alcohol use in patients with cirrhosis is associated with a significant increase of the secondary bile acids compared with abstinent alcoholic cirrhosis and AALD (87). Patients with alcoholism have increased serum bile acids, cholestatic liver injury, and bile acid pool size and have reduced biliary bile flow and reduced fecal excretion. However, the role of bile acids in AALD is controversial and not understood. It has been reported that chronic or binge alcohol feeding induced *Cyp7a1* and enlarged the bile acid pool in mice (18). In rats, alcohol feeding significantly reduced taurine-conjugated bile acids in the liver and gastrointestinal tracts, increased expression of bile acid synthesis and efflux genes, and decreased bile acid uptake transporter (210). Chronic ethanol feeding in mice induced the expression of bacteria expressing cholyglycine hydrolase, increased unconjugated bile acids, lowered FGF15, and increased *Cyp7a1* (69). These effects and symptoms of alcoholic liver disease were reduced with antibiotics or administration of an FXR-specific agonist (69). These studies suggest that alcohol stimulates bile acid synthesis to increase bile acid pool size and cause cholestatic liver injury. In contrast, chronic plus binge alcohol feeding has been shown to reduce *Cyp7a1* expression but increase the bile acid pool by increasing intestinal bile acid reabsorption in wild-type mice, whereas it exacerbates liver injury in *Cyp7a1*^{-/-} mice (39). A recent

analysis of the serum metabolome of patients with alcoholism identified increased serum levels of GCDCA, TCDCA, GCA, and TCA, which were positively correlated with AALD progression (213). Interestingly, this study found that liver CYP7A1 levels were decreased but that CYP7B1 levels were increased in AALD. They also found that serum GLP-1 and FGF21 levels but not FGF19 levels were increased in patients who drank heavily. Another recent study of patients with AALD found that alcohol drinking decreased hepatic bile acid synthesis but increased serum bile acids and FGF19 levels, which were positively correlated to the severity of AALD (13). This study also confirmed that bile acid synthesis is reduced in patients with AALD and not increased as previously thought by many investigators. There is no effective drug therapy for AALD. Several recent studies reported that FXR and TGR5 agonists ameliorated liver injury, steatosis, and inflammation in mouse models of binge and prolonged alcohol feeding (79, 207). These studies suggest that bile acid homeostasis is dysregulated in AALD, and modulation of bile acid signaling and/or the gut microbiota might be promising strategies for treating alcoholic hepatitis.

BILE ACID-BASED THERAPIES FOR FATTY LIVER DISEASES

Bile acid-based therapies targeting FXR and TGR5 were first developed to treat rare cholestatic liver diseases, including primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC). PBC is an acquired chronic cholestasis associated with autoimmune destruction of the small bile ducts, portal infiltration, and fibrosis. PSC is associated with liver injury and fibrosis of both intrahepatic and extrahepatic bile ducts, resulting in biliary strictures and obstructed bile flow. These bile acid drug therapies have been extended to clinical trials for NASH and AALD and are based on the anti-inflammatory effects of the activation of FXR and TGR5 signaling in liver, adipose tissue, and intestine in mouse models of diet-induced obesity, insulin resistance, and NAFLD. Targeting FXR and TGR5 signaling has been shown to improve hepatic bile acid metabolism and lipid and glucose homeostasis to prevent progression of NASH in clinical trials. Both activation and antagonism of intestinal FXR alleviate diet-induced obesity and diabetes. Table 1 summarizes bile acid-based therapies for NAFLD.

FXR Agonists

Obeticholic acid (OCA) (OCALIVA, 6 α -ethyl-CDCA, EC₅₀ = 0.099 μ M) improved NASH scores in human patients with PBC who had inadequate responses to UDCA and in patients with T2DM and NASH without cirrhosis (71, 98, 123, 128, 129). However, an unwanted side effect of OCA is increased serum LDL cholesterol and decreased HDL cholesterol, and pruritus is a common side effect of bile acid therapy (142). OCA increased FGF19 in the gallbladder to reduce emptying, decrease bile acid synthesis, and increase bile acid hydrophobicity and cholesterol saturation index in patients with gallstone disease (1). OCA has been shown to improve NASH (128), and the third-phase clinical trial of OCA for treatment of NASH with fibrosis has shown significant improvement of fibrosis by one stage. Nonsteroidal FXR ligands have been developed for clinical trials for liver diseases (60). Cilofexor (GS-9674 derived from GW4064) has been shown to

Table 1. *Bile acid-based therapies*

	Treatment
Bile acids	
CA (Cholbam) and CDCA (Chenodiol)	Treats inborne errors of bile acid synthesis; dissolves gallstones
UDCA (Ursodiol®, Actigall)	Dissolves gallstones; reduces bile acid cytotoxicity
NorUDCA	PSC
Bile acid sequestrants	
Cholestyramine, Colesevelam	Dissolves gallstones; reduces bile acid pool and stimulates bile acid synthesis; decreases FGF19; activates TGR5/GLP-1 and improves glycemic control; stimulates thermogenesis in BAT; BAD
FXR agonists: anti-inflammation, cholestasis, NASH fibrosis, diabetes, obesity	
OCA (OCALIVA)	PBC and BAD
Fexaramine (intestine-restricted FXR agonist)	stimulates adipose tissue browning, stimulates GLP-1 secretion, improves insulin sensitivity and reduces weight
FXR antagonists (intestine)	
GUDCA, Gly-MCA	PBC; reduces weight, improves diabetes
FGF19 analog	
NGM282	anti-inflammation and fibrosis; NASH
Nonsteroidal FXR agonists	
Cilofexor, Tropicifexor	PBC and NASH

BAD, bile acid diarrhea; BAT, brown adipose tissue; CA, cholic acid; CDCA, chenodeoxycholic acid; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide-1; Gly, glycine; GUDCA, glyco-ursodeoxycholic acid; MCA, muricholic acid; NASH, nonalcoholic steatohepatitis; OCA, obeticholic acid; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; TGR5, Takeda G protein-coupled receptor 5; UDCA, ursodeoxycholic acid.

improve cholestasis and liver injury in a phase two clinical trial of PSC (191), and the non-bile acid FXR agonist tropifexor (LJN452) reversed fibrosis and reduced hepatic steatosis and triglycerides in mice (192) and is currently in phase 2B trials for the treatment of NASH and PBC in humans (140). Recently, OCA has been used to treat bile acid diarrhea (BAD), possibly by stimulating FGF19 (75, 101, 199). BAD results from excessive colonic bile acids caused by ileal resection, inflammatory injury, and inflammatory bowel diseases (IBDs) (14).

FXR Antagonists

Most recent studies show that FXR antagonism may have therapeutic value for treating NAFLD. UDCA (Ursodiol, Actigall), a weak FXR antagonist, has been shown to reduce ER stress and restore glucose homeostasis in a mouse model of T2DM (130). UDCA stimulated bile acid synthesis by reducing FGF19 and depleting hepatic LDL cholesterol but induced liver stearoyl-CoA desaturase-1 to increase liver triglycerides in a small trial of patients with NAFLD and morbid obesity (124). The antidiabetic drug metformin reduces *Bacteroides fragilis* and increases G-UDCA in patients with diabetes in 3 days (182), suggesting that metformin may alter the gut microbiota to antagonize intestinal FXR via UDCA and improve metabolism during diabetes.

TGR5 Agonists

The TGR5-selective agonist INT-777 (6 α -ethyl-23(*S*)-methylcholic acid, EC₅₀ = 0.82 μ M) stimulates adipose tissue thermogenesis and energy metabolism, reduces inflammation (141), and stimulates GLP-1 secretion and insulin sensitivity but does not affect serum lipids (138). INT-777 may have anti-inflammasome effects in pancreatic acinar cells and may also reduce neuroinflammation (104, 208). A derivative of UDCA, BAR501 (6 β -3 α , 7 β -dihydroxy-5 β -cholan-24-ol), has been shown to reduce lipid deposition and vascular injury in DIO mice and regulate natural killer T cells during hepatitis (9, 173). Another selective TGR5 agonist, RDX8940, improved hepatic steatosis and insulin sensitivity with minimal systemic effects in Western diet-fed mice (49). However, activation of TGR5 may also induce unwanted side effects, including inhibition of gallbladder emptying and gallstone formation (195) and change of heart rate and blood pressure (146).

Dual FXR and TGR5 Agonists

The bile acid derivative 6 α -ethyl-3 α , 7 α , 23-trihydroxy-24-nor-5 β -cholan-23-sulfate sodium salt (INT-767) is an FXR (EC₅₀ = 0.03 μ M) and TGR5 (EC₅₀ = 0.63 μ M) dual agonist. INT-767 is a more potent FXR agonist than OCA and is in a phase one clinical trial for NASH. INT-767 reduced expression of classic pathway bile acid synthesis genes but induced those in the alternative pathway to decrease TCA and increase T-MCA in mice (138). INT-767 induced intestinal FXR expression and intracellular Ca²⁺ and cAMP activity to stimulate GLP-1 secretion and improve glucose and lipid metabolism in DIO mice. BAR502, a nonsteroidal dual FXR and TGR5 agonist, promotes white adipose tissue browning and reverses high-fat diet-induced hepatic steatosis and fibrosis in mice (15).

FGF19 and FGF21

Drugs targeted to the prevention of the progression of simple steatosis to NASH are being developed. Serum FGF19 levels increase after bariatric surgery and are associated with improvement of glycemic control and diabetes remission in patients with obesity and diabetes, suggesting that targeting FXR and FGF19 may have therapeutic potential for treating NASH and HCC (11, 61). However, as a growth factor, FGF19 increases tumorigenesis when highly expressed at nonphysiological levels (221). A nontumorigenic FGF19 derivative, NGM282, reduced *Cyp7a1* expression, bile acid pool size, and hepatic inflammation and improved NASH fibrosis in 12 wk of clinical trials (68). FGF21 reduces serum triglycerides by stimulating lipolysis in white and brown adipose tissues in mice (172). A long-lasting FGF21 analog, PF-05231023, has been shown to reduce body weight and improve lipid profile in patients with T2DM (187). FGF21 analogs are currently in clinical trials for obesity and T2DM.

Bile Acid Sequestrants

Bile acid sequestrants are a class of drugs that bind negatively charged bile acids in the intestine to prevent bile acid reabsorption and reduce bile acid pool size. This results in reduced FGF15 and increased *CYP7A1* gene transcription and hepatic bile acid synthesis. Cholestyramine and colestipol are

classic bile acid sequestrants used to treat cholesterol gallstone disease and hypercholesterolemia in human patients. Colesevelam and colestimide are second-generation bile acid sequestrants that have been shown to improve glycemic control in T2DM (50a). Bile acid sequestrants may increase secondary bile acids in the colon to stimulate TGR5-mediated secretion of GLP-1 and TGR5-mediated thermogenesis in brown adipose tissue and beiging of white adipose tissue (151, 174). By increasing bile acid synthesis to reduce hepatic cholesterol, bile acid sequestrants increase hepatic LDL-cholesterol uptake, reduce serum cholesterol, and protect against cardiovascular disease. Bile acid sequestrants also have been used to treat BAD and IBD (Crohn's disease) by reducing intestinal bile acid reabsorption (14, 205). However, bile acid sequestrants have the unwanted side effects of increasing serum triglycerides and dyslipidemia.

Probiotics

Targeting the gut microbiota using probiotics and nondigestible fermentable carbohydrates (prebiotics, fermentable dietary fibers, and microbiota-accessible carbohydrates) has been shown to improve health and metabolic diseases (34, 194). Probiotics are live microorganisms that may provide benefits for HCC, NASH, and IBD by modifying the gut microbiota (12). *Lactobacillus* with active BSH activity in yogurt reduces serum cholesterol in human trials (83, 84). Probiotic VSL 3 induces BSH activity to promote bile acid deconjugation and increase bile acid synthesis by inhibiting the FXR-Fgf15 axis, thus increasing fecal bile acid excretion to improve insulin signaling and protecting against NASH in mice (35, 120). *Bifidobacterium* and *Lactobacillus* are commonly used as probiotics to improve intestinal barrier function (121). *Akkermansia*, *Eubacterium* and *Faecalibacterium* also have beneficial effects for diabetes and Crohn's disease (31, 42, 176). *Clostridia* and *Bacteroides* are associated with intestinal infection but are used as probiotics for patients with colitis (6, 165). *Bacteroides fragilis* is a commensal bacterium that alters the gut microbiome, induces TGR5/GLP-1, and promotes adipose tissue browning to reduce weight. *Bacteroides acidifaciens* improves obesity and insulin sensitivity by increasing GLP-1 and decreasing intestinal dipeptidyl-4 in mice (212). This effect is apparently mediated through activation of TGR5 signaling. However, these over-the-counter probiotics have not been tested rigorously for their claimed beneficial metabolic effects and safety. A recent exploratory study shows that supplementation with *Akkermansia muciniphila* improved gut-barrier function and insulin sensitivity and reduced plasma total cholesterol in patients with T2DM who were overweight (37). This proof-of-concept study shows supplementation of *Akkermansia muciniphila* is safe and well tolerated to improve metabolic parameters.

Bariatric Surgery

Bariatric surgeries, such as Roux-en-Y gastric bypass and vertical sleeve gastrectomy, are the most effective treatments for reducing weight (11). In patients with T2DM, serum FGF19 levels are lower, whereas serum FGF21 levels are higher. Many studies demonstrate that bariatric surgery increases serum bile acids and FGF19 levels, which are associated with rapid improvement of insulin resistance in patients

with obesity (11, 127, 152, 163, 177). Interestingly, serum FGF19 in individuals with obesity increased after bariatric surgery but not after conventional diet-induced weight loss (62). Serum FGF19 levels coincide with increased serum bile acids and GLP-1 following bariatric surgery (1a). The mechanisms by which bile acids improve glycemic control following gastric bypass may involve FXR signaling in glucose metabolism and/or TGR5 signaling in energy metabolism and insulin sensitivity. The greater increases in unconjugated and glycine-conjugated primary bile acids after duodenal switch compared with gastric bypass suggest that a constitutively increased bile acid pool may be due to shorter enterohepatic circulation of bile acids, which alters the gut microbiome and metabolites to improve the metabolism. Another recent study of serum bile acid profiles following gastric bypass and duodenal switch surgeries over 5 yr showed substantial increase of total serum bile acid concentration, likely via activation of both FXR and TGR5 signaling (163). Both primary and secondary bile acid levels are higher in subjects with insulin resistance and obesity and are positively correlated to insulin-resistance markers, and sleeve gastrectomy reduces total conjugated and unconjugated CA and increases LCA (33). This finding may suggest that increasing LCA can stimulate TGR5/GLP-1 signaling to improve glycemic control after sleeve gastrectomy. A systemic review and meta-analysis showed that bariatric surgery completely resolved NAFLD in patients with obesity (103). Thus, alteration of the gut microbiota and bile acid metabolism may be a major contribution to the metabolic benefits of bariatric surgery.

CONCLUSIONS AND FUTURE PERSPECTIVES

Significant progress in basic research of bile acid metabolism and signaling has been made in the last three decades. The roles and mechanisms of bile acid signaling in the pathophysiology of metabolic diseases have been unveiled with the use of genetic and diet-induced mouse models of cholestasis, diabetes, and obesity. Current trends in liver research are focused on the pathogenesis of NAFLD, especially the progression of nonfibrotic NASH to fibrotic NASH, cirrhosis, and HCC. Importantly, basic liver research has been translated to bile acid-based drug therapies for the treatment of NASH, diabetes, and obesity; although some bile acid derivatives may induce unwanted side effects, such as pruritus and cardiovascular and gallbladder-emptying effects. FXR agonists have been successfully approved for treating PSC and PBC, which are rare liver diseases. Many bile acid-based FXR agonists and nonsteroidal FXR agonists are in clinical trials, and it is anticipated that FXR agonists will be approved for treating NASH fibrosis in the near future. Dysbiosis appears to be a significant risk factor for the pathogenesis of diabetes, obesity, and NAFLD. Directly targeting gut dysbiosis with dietary management and probiotic and prebiotic supplements may be a potential strategy for treating liver-related disease. However, further studies are needed to identify serum bile acids, metabolites, and gut species as markers for diagnosis, treatment, and prevention of diabetes, obesity, NASH, and AALD.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

J.C. and J.M.F. conceived and designed research; J.C. analyzed data; J.M.F. interpreted results of experiments; J.C. prepared figures; J.C. and J.M.F. drafted manuscript; J.C. and J.M.F. edited and revised manuscript; J.C. and J.M.F. approved final version of manuscript.

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